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The role of primary antifungal prophylaxis in patients with haematological malignancies

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Abstract

Invasive fungal infections (IFIs) represent important complications in patients with haematological malignancies. Chemoprevention of IFIs may play an important role in this setting, but in the past decades the majority of antifungal drugs utilized demonstrated poor efficacy, particularly in the prevention of invasive aspergillosis. The new triazoles are very useful antifungal drugs, more suitable for prophylaxis of IFIs than amphotericin B and echinocandins. In this review, the main clinical data about antifungal prophylaxis with fluconazole, itraconazole, voriconazole and posaconazole are analysed. At present, posaconazole appears to be the most efficacious azole in antifungal prophylaxis, particularly in patients with acute myeloid leukaemia.

Keywords: antifungal prophylaxis, fluconazole, itraconazole, leukaemia, posaconazole, stem cell transplantation, voriconazole
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Epidemiology of Fungal Infections in Haematology

Invasive fungal infections (IFIs) are a leading infectious cause of morbidity and mortality in patients with haematological malignancies [1]. Patients with haematological malignancies such as acute leukaemia, myelodysplastic syndromes and those undergoing allogenic haemopoietic stem cell transplant (allo-HSCT) are at major risk of IFIs [2]. In particular, the incidence of IFIs is higher in acute myeloid leukaemia (AML) [3]. In the recent past, some studies evaluated the incidence and outcome of IFIs in haematological malignancies. A retrospective study, conducted in a population of 11 802 haematological malignancies treated with conventional chemotherapy, showed an overall incidence of 4.6% proven/probable IFIs, but the incidence of IFIs was highest among patients with AML (*c.* 8%). In some settings, IFIs caused by moulds are more frequent than those caused by yeasts, and *Aspergillus* spp is the most common pathogen [4]. The risk of invasive aspergillosis (IA) is not constant over all the phases of AML treatment: the majority of AML patients usually experience IA after the first cycle of chemotherapy (1st induction), the first time that a colonized patient experiences deep immunosuppression. An IFI during the first induction may dramatically compromise the following therapeutical strategy for AML [5].

For this reason, antifungal prophylaxis of IFIs may have an important role in this setting; in the past decades, chemoprophylaxis with oral polyenes and old triazoles showed poor efficacy. At present, the availability of new triazoles (i.e. voriconazole, posaconazole) characterized by a wider spectrum may have modified the role of antifungal prophylaxis. In this review, the efficacy of the different antifungal prophylaxis used over the years will be analysed.

Past Role of Chemoprophylaxis

Several review articles evaluated the role of the prophylaxis of IFIs in the pre-new antifungals era [6–10]. Topical therapy with

oral polyenes has the potential to prevent candidiasis with less risk of side effects and drug interactions than systemic therapy. It has been found useful in prevention of serious *Candida* infection in high-risk patients [9,10]. However, this kind of prophylaxis has been disappointing, particularly against *Aspergillus*.

Some years ago, Uzun and Anaissie described some criteria to identify the optimal antifungal agent. The ideal prophylactic agent should be safely administrable over long periods, effective, fungicidal against a wide spectrum of fungal pathogens, inexpensive, available in both oral and intravenous formulation and associated with a low incidence of resistance [11]. These criteria identified triazoles as a very useful class of oral antifungal drugs, more suitable for chemoprophylaxis of IFIs than AmB and other drugs, available only in intravenous (iv) formulation.

Fluconazole

Fluconazole was the first azole systematically used for chemoprophylaxis of IFIs. Due to its high systemic activity and low toxicity, fluconazole facilitated an earlier and prophylactic use of systemic antifungals, and it is not contraindicated in patients receiving cyclosporine prophylaxis against graft-versus-host disease (GVHD). However, it appears effective only in high doses, commonly associated with adverse reactions [6–8]. Fluconazole is active against the most of *Candida* strains, although some strains are inherently resistant (i.e. *Candida kruzei or Candida glabrata*) [12].

Randomized, double-blind, placebo-controlled trials evaluated fluconazole as antifungal prophylaxis for HSCT recipients. Goodman *et al.* studied 356 autologous and allo-HSCT recipients from multiple centres, using fluconazole (400 mg/day) or placebo from the start of the conditioning period for a maximum of 10 weeks. IFIs occurred in 28 patients who received placebo as compared with five who received fluconazole (15.8% vs. 2.8%, $p < 0.001$). Fluconazole prevented infection with all species of *Candida* except *C. krusei*. Fewer infection-related deaths occurred in the fluconazole arm of the study (1/179 vs. 10/177, $p < 0.001$), but fluconazole did not significantly alter overall mortality [13]. In a second study, Slavin and coworkers sought to determine whether a longer course of prophylaxis with fluconazole would improve survival or lower the incidence of infections. They administered fluconazole (400 mg/day for 75 days) to allo-HSCTs. The rate of IFIs in the fluconazole arm during prophylaxis was 10/152 patients (7%) vs. 26/148 patients (18%) in the placebo arm (p 0.004). The rate of IFI-related deaths by day 110 after transplant was 13% in the fluconazole arm and 21% in the placebo arm (p 0.005). In contrast to the Goodman study, at day 110, the probability of overall survival was improved among fluconazole recipients (20% vs. 35%, $p = 0.004$) [14]. However, it is noteworthy that at time of these studies, *Candida* spp. caused the majority of IFI, and this may explain fluconazole's good performance.

A post-mortem study carried out on 720 patients given fluconazole prophylaxis showed that they died of *Candida* infection less frequently than of *Aspergillus* IFI; however, it must be taken in account that the sensitivity of blood cultures decreased when patients received fluconazole prophylaxis, a possible evaluation bias. [15]. Several authors demonstrated that the intensive use of fluconazole prophylaxis in haematological malignancies selected multiresistant and difficult-to-treat species of *Candida* non-*albicans* [4,16–19]. Recent nationwide data in Denmark reported an increasing incidence of candidemia associated with a decreasing proportion being susceptible to fluconazole. The fluconazole MICs for *C. glabrata* and *C. krusei* were in general elevated compared with those for *C. albicans*; for *C. glabrata* in particular, the MIC distribution suggests acquired resistance mechanisms for a proportion of isolates [20].

Itraconazole

In contrast to fluconazole, itraconazole is active against *Aspergillus* spp; two studies compared the prophylactic activity of these two drugs in haematological patients undergoing allo-HSCT. In the first study, itraconazole in oral solution form was administered, and a significant reduction in IFIs incidence with itraconazole without differences in fungal-free survival was observed [21]. In a second study, itraconazole was administered initially intravenously and then as oral solution, and resulted in fewer proven IFIs and lower fungal-related mortality, but similar overall mortality, compared to fluconazole after allo-HSCT [22]. In both studies, mild gastrointestinal side effects in itraconazole arm were observed.

The study of the GIMEMA-infection group (Gruppo Italiano Malattie Ematologiche dell'Adulto) that compared itraconazole oral solution to placebo, did not show advantage to itraconazole regarding the incidence of invasive aspergillosis, but a significant reduction in candidemia was observed [23].

However, an interesting meta-analysis evaluated the efficacy of itraconazole vs. other forms of prophylaxis for the prevention of IFIs in neutropenic cancer patients after chemotherapy or allo-HSCT. The meta-analysis of 13 randomized trials in 3597 neutropenic patients with haematological malignancies showed a significant reduction in the incidence of IFIs (p 0.002), of invasive yeast infections (p 0.004) and mortality from IFIs (p 0.04), with a highly significant dose–response relationship [24].

The use of itraconazole as prophylaxis is limited by the poor drug absorption, when given in capsules, and by the gastrointestinal side effects, when given as oral suspension [21,22].

The New Triazoles

Voriconazole

Voriconazole is available for clinical use since 2003 and was initially used for the targeted treatment of *Aspergillus* spp. infections. Some recent clinical trials tried to demonstrate its efficacy also as antifungal prophylaxis. A multicenter, randomized, double-blind trial compared fluconazole ($N = 295$) vs. voriconazole ($N = 305$) for 100 days (180 days in higher-risk cases) for the prevention of IFIs in patients undergoing myeloablative allo-HSCT. Despite a nonsignificant trend for fewer *Aspergillus* infections in favour of voriconazole (9 vs. 17, p-value 0.05), the authors reported no significant differences in IFI incidence (7.3% vs. 11.2%), and empiric antifungal therapy use (24.1% vs. 30.2%), while fungal-free survival rates (75% vs. 78%) at 180 days and overall survival were similar between fluconazole and voriconazole [25]. The prospective, randomized, open-label, multicentre study by Marks *et al.* compared the efficacy and safety of voriconazole (234 patients) vs. itraconazole oral solution (255 patients) in allo-HSCT recipients. The efficacy of prophylaxis was significantly higher with voriconazole than itraconazole (48.7% vs. 33.2%, $p < 0.01$); itraconazole patients received more often other systemic antifungals (41.9% vs. 29.9%, $p < 0.01$) but more patients tolerated voriconazole prophylaxis for 100 days (53.6% vs. 39.0%, $p < 0.01$). However, no difference in terms of incidence of proven/probable IFIs (1.3% vs. 2.1%) or survival to day 180 (81.9% vs. 80.9%) was observed for voriconazole and itraconazole, respectively [26].

These studies failed to show significant benefit for voriconazole compared with itraconazole or fluconazole in antifungal prophylaxis.

Posaconazole

Posaconazole, available for clinical use since 2007, is a new-generation oral azole with *in vitro* activity against a wide spectrum of medically important fungi, including *Candida* spp., *Aspergillus* spp., *Zygomycetes* and *Fusarium* [27]. *In vitro* susceptibility may vary among *Zygomycetes* and *Fusarium species,* and there are no *in vivo* data on the efficacy against these rare fungi [28–30].

A randomized, multicenter single-blind study conducted by Cornely *et al.*, evaluated the efficacy and safety of posaconazole ($n = 304$) compared to fluconazole ($n = 240$) or itraconazole ($n = 58$) as prophylaxis for each cycle of chemotherapy (until recovery from neutropenia and complete remission or for up to 12 weeks) in patients with AML or myelodysplastic syndrome and prolonged neutropenia. The primary endpoint was the incidence of proven/probable IFIs during treatment, and the secondary endpoints were death from any cause and time to death. As far as the primary endpoint is concerned, proven/probable IFIs were observed in seven patients (2%) in the posaconazole group and 25 patients (8%) in the pooled standard triazoles group (absolute reduction in the posaconazole group, -6%; 95% confidence interval, −9.7 to −2.5%; $p < 0.001$) during the on-treatment period (from randomization to 7 days after the last dose of study drug). Significantly fewer patients in the posaconazole group had invasive aspergillosis (2 [1%] vs. 20 [7%], $p < 0.001$). Posaconazole maintained superiority over pooled standard triazoles in preventing IFIs during the 100-day period after randomization: 14/304 (5%) vs. 33/298 (11%), p 0.003. Posaconazole was also significantly better than pooled standard triazoles in preventing IA during the treatment phase (2 [1%] vs. 20 [7%], $p < 0.001$) and during the 100-day period after randomization or fixed time period (4 [1%] vs. 26 [9%], $p < 0.001$). Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole (p 0.04). Serious adverse events possibly or probably related to treatment were reported by 19 patients (6%) in the posaconazole group and six patients (2%) in the fluconazole or itraconazole group (p 0.01) [27].

In another randomized double-blind trial, Ullmann *et al.* compared oral posaconazole with oral fluconazole for prophylaxis against IFIs in 600 allo-HSCT recipients with GVHD treated with immunosuppressive therapy. At the end of the fixed treatment (day 112), the difference in incidence of all proven/probable IFIs between posaconazole and fluconazole arms was not significant (5.3% and 9.0%, respectively; p 0.07), but posaconazole was superior to fluconazole in preventing proven/probable IA (2.3% vs. 7.0%; p 0.006). During the exposure period (time from first dose to 7 days after the last dose), posaconazole significantly reduced the incidence of breakthrough proven/probable IFIs (2.4% vs. 7.6%, p 0.004) and IA (1.0% vs. 5.9%, p 0.001) vs. fluconazole. Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%, vs. 4% in the fluconazole group; p 0.046). The incidence of treatment-related adverse events was similar in the two groups, such as the rates of treatment-related serious adverse events (13% and 10%, respectively) [31].

Posaconazole demonstrated to be clinically superior to other triazoles in preventing IFIs (especially aspergillosis)

among immunocompromised hosts. Furthermore, some economical models reported posaconazole prophylaxis to be a cost-effective strategy compared to old triazoles in high-risk patients [32–34].

At present, posaconazole is only available in oral formulation, and this has been associated with high interpatient (up to 68% in adult patients) and intrapatient variability of drug bioavailability [35,36]. Monitoring of drug plasma levels should be performed whenever possible, in particular in patients with impaired gastrointestinal absorption (due to diarrhoea, mucositis, poor oral intake, vomiting) or in patients receiving drugs known to either impair absorption or increase clearance (i.e. proton pump inhibitors) [37].

Intravenous Prophylaxis

Deoxycolate AmB is not indicated as prophylaxis, due to its relevant nephrotoxicity and poor efficacy [38].

Caspofungin was the first antifungal echinocandin to be used for prophylaxis in patients with haematological malignancies. The efficacy and safety of caspofungin were similar to other prophylactic regimens, and no great advantage in its use was demonstrated [39,40]. In the study by Mattiuzzi *et al.* [39] on 200 patients with haematological malignancies, intravenous itraconazole and caspofungin provided similar protection against IFIs during induction chemotherapy, and both drugs were well tolerated. Similarly, the PROFIL-C study comparing caspofungin to standard prophylaxis (mainly itraconazole) did not show any advantage in terms of IFI incidence, IA incidence, IFI-related mortality and safety [40]. On the contrary, the analysis of data from a multinational case registry by Vehreschild *et al.* [41] showed a possible role of caspofungin as secondary antifungal prophylaxis.

A prospective, randomized, double-blind comparative trial study showed that micafungin compared with fluconazole seems to be a valid therapeutical option for prophylaxis particularly in patients undergoing autologous or allo-HSCT. The overall efficacy of micafungin was superior to that of fluconazole during the neutropenic phase after HSCT [42]. In another prospective study that compared micafungin with itraconazole oral solution, non-inferiority of micafungin regarding IFIs was observed [43]. Similar results were observed in a prospective study where micafungin was compared with a historical control of patients treated with fluconazole [44].

Some studies demonstrated the feasibility and safety of a single weekly very high dose of liposomal AmB as antifungal prophylaxis both in adult patients with acute myeloid leukaemia patients undergoing induction chemotherapy and immunocompromised children [45,46]. Results of these studies are interesting but based on very small series.

Meta-analysis and Guidelines

A meta-analysis published by Robenshtok *et al.* in 2007 evaluated the effect of antifungal prophylaxis on all-cause mortality as primary outcome, IFIs, and adverse events in 64 randomized, controlled trials comparing systemic antifungals with placebo, no intervention, no systemic antifungal prophylaxis in cancer patients after chemotherapy.

At the end of follow-up, antifungal prophylaxis significantly decreased all-cause mortality (RR 0.84; 95% CI 0.74–0.95). In particular, in allo-HSCT recipients, prophylaxis reduced all-cause mortality (RR 0.62; 95% CI 0.45–0.85), IFI-related mortality (RR 0.52; 95% CI 0.27–0.74) and documented IFIs (RR 0.50; 95% CI 0.41–0.99). In acute leukaemia patients, there was a significant reduction in documented IFIs (RR 0.69; 95% CI 0.53–0.90), whereas the difference in mortality (RR 0.88; 95% CI 0.74–1.06) and IFIs-related mortality (RR 0.66; 95% CI 0.44–1.00) was only borderline significant. In particular, prophylaxis with itraconazole suspension reduced documented IFI when compared to fluconazole, with no difference in survival but with more adverse events [47].

A more recent meta-analysis analysed 20 trials comparing systemic mould-active vs. fluconazole prophylaxis in cancer patients receiving chemotherapy or allo-HSCT. Study regimens included amphotericin B formulations ($n = 4$), micafungin ($n = 3$), posaconazole ($n = 2$), voriconazole ($n = 1$) and itraconazole ($n = 10$). The analysis confirmed that mould-active prophylaxis is preferable, due to a significant reduction in the number of proven/probable IFI (RR 0.71; 95% CI 0.52–0.98; p 0.03), of invasive aspergillosis (RR 0.53; 95% CI 0.37–0.75; p 0.0004) and IFI-related mortality (RR 0.67; 95% CI 0.47–0.96; p 0.03) [48].

Based on these data, most of the clinical guidelines on antifungal prophylaxis in AML and allo-HSCT recommend posaconazole as antimould prophylaxis in immunocompromised patients, especially after chemotherapy (Table 1) [49–54]. IDSA guidelines recommend prophylaxis against *Candida* spp in high-risk patients (acute leukaemia and allo-HSCT) (evidence A-1) and consider fluconazole, itraconazole, voriconazole, posaconazole, micafungin and caspofungin all acceptable alternatives. Posaconazole is recommended as prophylaxis against *Aspergillus* spp in those patients who are undergoing intensive chemotherapy for acute myeloid leukaemia or myelodysplastic syndrome (evidence B-1) [51].

TABLE 1. Therapeutical recommendation by International Guidelines on antifungal prophylaxis in AML and allo-HSCT [47–49]

	FLUCO	VORICO	ITRA	POSA	CASPO	L-AmB	MICA
ECIL-3–4 [49]							
CT	C-I	–	C-I	A-I	–	C-I	–
Allo-HSCT	A-I	A-I	B-I	A-I	–	C-I	C-I
DGHO [50]							
Neutropenic	C-I	CII	C-I	A-I	C-I	C-II	–
Allo-HSCT	A-I	CII	C-I	A-I	–	–	C-I
IDSA [51] (against *Candida*)							
AL	A-I	–	A-I	A-I	A-I	–	A-I
Allo-HSCT	A-I	–	–	A-I	–	–	A-I
IDSA [51] (against *Aspergillus*)							
AML-MDS	–	–	–	B-I	–	–	–
British guidelines [52]	–	–	B-II	A-I	–	B-II	–
NCCN [53]							
AML-MDS	2B	2B	–	I	–	2B	–
Allo-HSCT	I	2B	2B	2B	–	2B	I
ESCMID [54]							
Neutropenic allo-HSCT	A-I	A-I	B-I	A-II	C-II	B-II/C-III	A-I/C-I

AML, acute myeloid leukaemia; allo-HSCT, allogenic haematopoietic stem cell transplant; MDS, myelodysplastic syndrome; FLUCO, fluconazolo; VORICO, voriconazole; ITRA, itraconazole; POSA, posaconazole; CASPO, caspofungin; L-AmB, liposomal Amphotericin B; MICA, micafungin, CT, chemotherapy; ECIL, European Conference on Infections in Leukaemia; DGHO, German Society for Haematology and Oncology; IDSA, Infectious Diseases Society of America; NCCN, National Comprehensive Cancer Network; ESCMID, European Society of Clinical Microbiology and Infectious Diseases.

From Bench to Bedside

The main limitation of randomized controlled trials is that they usually enrol 'healthy' patients and thus results cannot be confirmed in a real-life setting of unselected patients. For this reason, real-life studies may be of help in assessing whether results from randomized clinical trials can be translated into clinical practice.

In the last few years, some real-life experiences confirmed the efficacy of posaconazole prophylaxis in this clinical setting, even if they were almost all retrospective studies and with historical comparisons (Table 2) [33,57–64].

The recent prospective registry by SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne) analysed the efficacy of antifungal prophylaxis with posaconazole (n = 260) and itraconazole (n = 93) in a large series of consecutive patients with AML during the first induction of remission. The results of this real-life study confirmed those by Cornely's trial: there were significant differences in favour of posaconazole vs. itraconazole in terms of breakthrough IFIs rate (18.9% vs. 38.7%, $p < 0.001$), proven/probable mould infections rate (2.7% vs. 10.7%, p 0.02), mould-attributable (0 vs. 4.3%, p 0.005) and overall mortality rate (3.5% vs. 9.7% p 0.02) [61].

De Pauw *et al.* highlighted the ability of posaconazole to suppress serum galactomannan (GM) expression, the more useful parameter for identifying an IA [65,66], According to several studies, sensitivity and diagnostic utility of GM may be compromised during receipt of prophylactic or empirical antifungal therapies [67–71]. This may explain why the SEIFEM study showed a higher use of empirical than pre-emptive therapy, after posaconazole prophylaxis [61].

Plasma therapeutic levels of posaconazole were not evaluated in the randomized clinical trials nor in the SEIFEM study [50,61]; however, an *in vitro* study demonstrated that rapid drug clearance makes difficult a correct kinetic evaluation and

TABLE 2. Incidence of proven/probable (according to current EORTC/MSG diagnostic criteria) invasive fungal infections in acute myeloid leukaemia after posaconazole prophylaxis: data from comparative studies [adapted from 33,56–64]

	Posaconazole			Comparator					
	N° pts	Prov/prob IFIs (%)	Prov/prob IA (%)	DRUGS	N° pts	Prov/prob IFIs (%)	p-value	Prov/prob IA (%)	p-value
AML									
Michallet *et al.* [56]	55	—	2 (3.6)	None	66	—	nr	4 (6.1)	nr
Hahn *et al.* [57]	21[a]	1 (4.7)	—	fluco	21[a]	1 (4.7)	nr	—	nr
Egerer *et al.* [58]	76	1 (1.3)	1 (1.3)	nr	—	—		—	
Vehreschild *et al.* [59]	77	3 (3.9)	2 (2.6)	Topical polyenes	82	16 (19.5)	0.003	11 (13.4)	0.018
Ananda-Rajah *et al.* [60]	67	0	0	Fluco	36	6 (17)	nr	5 (13.9)	
				Itra	49	4 (8.2)		3 (6.1)	
				vorico	58	1 (1.7)		0	
Girmenia *et al.* [63]	99	23 (23.2)	15 (15.1)	Topical polyenes	58	30 (51.7)	0.0004	25 (43.1)	0.0002
Pagano *et al.* [61]	260	10 (3.8)	7 (2.7)	Itra	93	13 (14)	<0.001	9 (9.7)	0.02
Peterson *et al.* [64]	100	4 (4)	—	none	100	14 (14)	nr	—	
Allo-HSCT									
Sanchez-Ortega *et al.* [33] (days 0-100)	33	0	—	Itra	16	2 (12.5)	0.04	nr	nr
Chaftari *et al.*[b] [62]	21	0	—	wABLC	19	1 (5)	0.48	nr	nr
Hahn *et al.* [57] (Graft-vs-host disease)	15	1 (7)	—	fluco	8	2 (25)	nr	nr	nr

AML, acute myeloid leukaemia; wABCL, weekly lipid complex-Amphotericin B; nr, not reported; IFIs, invasive fungal infections; IA, invasive aspergillosis, allo-HSCT, allogenic haematopoietic stem cell transplant.
[a]Data on AML in first induction only.
[b]Early stop after interim analysis for safety reasons.

that the concentration of posaconazole in mammalian host cell membranes may represent a new mechanism to mediate drug efficacy. This may help in reinterpreting discrepancies between serum antifungal levels and efficacy [72].

Conclusion

Nowadays, antifungal prophylaxis in high-risk patients plays a relevant role, and thanks to the availability of newer drugs, better results are being reported in recent studies, both in randomized clinical trials and in 'real-life' studies. According to these data, posaconazole is now considered a promising option, particularly in AML patients. The role of diagnostic tools (i.e. GM, PCR) after posaconazole remains to be defined, as well as the optimal management of febrile neutropenia in those patients that received this kind of prophylaxis.

Transparency Declaration

LP has received honoraria from Gilead Sciences, Schering-Plough, Astellas Pharma, Merck and Pfizer Pharmaceuticals; he has been speaker for Gilead Sciences, Schering-Plough, Merck, Pfizer Pharmaceuticals, Astellas Pharma. MC has received honoraria from Gilead Sciences and Merck; she has been speaker for Gilead Sciences, Merck, Pfizer Pharmaceuticals, Schering-Plough, and Astellas Pharma.

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